Summary Basis for Regulatory Action

Date: July 10, 2012

From: Nancy Miller, M.D., Clinical Reviewer and Review Committee Chair

BLA/STN: 103606/5469

Applicant Name: Merck, Inc.

Date of Submission: June 20, 2011

PDUFA Goal Date: July 19, 2012

Proprietary/ Established Name:
VAQTA
Hepatitis A Vaccine Inactivated

Indication and Usage:
For use in children ≥ 12 months of age
For active immunization against disease caused by hepatitis A virus (HAV).

Recommended Action: APPROVAL

Signatory Authorities Action: Wellington Sun, M.D.
Director, Division of Vaccines and Applied Product Applications

Office's Signatory Authority:

√ I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

Material Reviewed/Consulted

Specific documentation used in developing the SBRA	Reviewer Name	Document Date
Clinical Review	Lorie Smith, M.D, M.H.S and Nancy Miller, M.D.	7/10/12
Statistical Review	Tammie Massie, Ph.D.	6/26/12
Serological Immune Response Assay Review/CMC Hepatitis A Diphtheria and tetanus *Haemophilus influenza b* Pertussis	 Marian Major, Ph.D. Leslie Wagner Margaret Bash, M.D. Juan Arciniega, D.Sc.	 12/16/11 6/15/12 6/18/12 3/15/12
Advertising and Promotional Labeling	Kristine T. Khuc, Pharm.D.	2/10/12
Bioresearch Monitoring Review	Dennis Cato	11/16/11, 2/10/12 and 6/14/12

In addition to the review documents listed above, records of meeting summaries and teleconferences, as well as e-mails exchanged internally and with the applicant were referenced.

1. Introduction

Supplemental Biologics License Application (sBLA) 103475/5469 was submitted by Merck, Inc. to fulfill two post-marketing commitments included in the approval letter for the VAQTA supplement dated August 11, 2005, in which the lower age of administration of VAQTA was changed from ≥ 2 years to ≥ 12 months of age. In the present supplement, clinical data were submitted to support the co-administration of VAQTA with diphtheria, tetanus, and acellular pertussis vaccine (DTaP) and *Haemophilus influenza b* vaccine (PedvaxHIB) as noted in Post-Marketing Commitment #4 of the August 11, 2005 approval letter. In addition, safety data for HAV-068, along with safety data from four additional previously submitted studies (HAV-043, HAV-057, HAV-066, and HAV-067) were submitted to support safety in at least 3000 children in the second year of life to fulfill Post-Marketing Commitment #1 of the August 11, 2005 approval letter.

The following major issues relevant to the review of sBLA 103606/5469, are discussed in this document:

a. Review of assays to assess serological responses to hepatitis A (HAV), diphtheria, tetanus and acellular pertussis (DTaP) and *Haemophilus influenza b* antigens (PedvaxHIB). The data were assessed as adequate for the purpose of demonstrating no evidence of interference in immune responses to hepatitis A and *Haemophilus influenza b* antigens when VAQTA was administered with Infanrix or PedvaxHIB or PedvaxHIB as compared to subjects receiving Infanrix and PedvaxHIB or PedvaxHIB without VAQTA. Similarly, there was no evidence of interference in immune responses to diphtheria toxoid and pertussis antigens [pertussis toxin (PT); filamentous hemagglutinin assay (FHA); and pertactin (PRN)] when VAQTA was administered with or without Infanrix (DTaP) and PedvaxHIB.

b. In the course of review of the tetanus assay for study 068, the CMC reviewer noted that two different assays were used during the course of the study. The assay change affected subjects tested from 2010 onward. CBER requested additional information regarding these assays. A post-hoc analyses was performed analyzing sera drawn from subjects pre- and post-vaccination with the same assay (i.e., both samples analyzed using either the older or the newer assay). The DTaP vaccination administered in study 068 represents the fourth dose of DTaP for these subjects. All subjects had anti-tetanus antibody levels ≥ 0.1 IU/mL at 4 weeks post-vaccination regardless of assays used or concomitant or non-concomitant vaccination status. Additionally, in the results of immune response to tetanus antigen in study 057 in subjects who had received VAQTA with or without Tripedia, there was no indication of interference with immune response to the fourth dose of tetanus. Therefore, CBER concluded that the package insert should include a statement to indicate there was no interference in immune response to tetanus (section 14.7).

c. No safety signals were noted in review of the combined safety data from studies 043, 057, 066, 067, and 068.

2. Background

Product Description

VAQTA is a sterile suspension containing an inactivated whole virus vaccine derived from hepatitis A virus grown in cell culture in human MRC-5 diploid fibroblasts. It contains inactivated virus of a strain which was originally derived by further serial passage of a proven attenuated strain. The virus is grown, harvested, purified, formalin inactivated, and then adsorbed onto aluminum hydroxyphosphate. Each 1-mL of vaccine contains 50U of hepatitis A virus antigen, which is purified and formulated without a preservative. Each 50U dose of vaccine contains less than 0.1μg of non-viral protein, less than 4×10^{-6} μg of DNA, less than 10^{-4} μg of bovine albumin, and less than 0.8 μg of formaldehyde. Other process chemical residuals are less than 10 parts per billion (ppb), including neomycin. Each 0.5 mL pediatric dose contains 25U of hepatitis antigen adsorbed onto 0.225 mg aluminum as amorphous aluminum hydroxyphosphate, and 35 μg of sodium borate as a pH stabilizer, in 0.9% sodium chloride. Each 1.0 mL adult dose contains 50U of hepatitis antigen adsorbed onto 0.45 mg aluminum as amorphous aluminum hydroxyphosphate, and 70 μg of sodium borate as a pH stabilizer, in 0.9% sodium chloride.

Regulatory History

VAQTA is a vaccine indicated for active immunization against disease caused by hepatitis A virus (HAV) for persons ≥ 12 months of age. VAQTA was initially licensed in persons ≥ 2 years of age in the Unites States (U.S.) in 1996. The protective efficacy and safety were evaluated in a randomized, double-blind, placebo-controlled (alum placebo) study involving 1037 susceptible healthy children and adolescents 2 through 16 years of age in a U.S. community with recurrent outbreaks of hepatitis A (Monroe Efficacy Study). In subjects who were initially seronegative for hepatitis A (presence of antibody to hepatitis A is considered a demonstration of protection against hepatitis A disease), the protective efficacy of a single dose of VAQTA against hepatitis A disease was 100%, with 21 cases occurring in the placebo group and zero in the VAQTA group. Duration of efficacy after two doses of VAQTA in a subset of subjects in the Monroe Efficacy Study has been documented to be nine years.

The age indication for VAQTA was extended to children as young as 12 months of age in 2005, based on demonstration of non-inferiority of immune response in children 12-23 months of age as compared to children 23-25 months of age (HAV-057), as well as comparability of safety profile in the two age groups. At the time the age indication was extended to children as young as 12 months of age (August 11, 2005), Merck agreed to evaluate the safety of administering two doses of VAQTA six months apart in an additional 3000 children 12 to 23 months of age. Three additional studies were specified as post-marketing commitment studies in that approval letter: 1) a study to evaluate the safety and immunogenicity of two doses of VAQTA in an additional 2260 subjects 12-23 months of age; 2) second study to evaluate the safety and immunogenicity of two doses of VAQTA when administered with or without pneumococcal 7-valent conjugate vaccine

(diphtheria CRM 197 protein) [Prevnar] and measles, mumps, rubella, varicella vaccine [ProQuad]; and 3) a third study to evaluate safety and immunogenicity of VAQTA when administered with or without diphtheria, tetanus toxoids, and acellular pertussis vaccine, adsorbed, DTaP [Infanrix] and *haemophilus influenza b* conjugate vaccine (tetanus toxoid conjugate) [PedvaxHIB]. The first two studies were previously submitted to the VAQTA BLA in an efficacy supplement, and resulted in the addition of data to the package insert (PI) for additional safety data for administration of VAQTA in subjects 12-23 months of age as well as inclusion of data for coadministration of VAQTA with Prevnar and Varicella [ProQuad] in sBLA 103606.5374 (approved March 25, 2010).

With this supplement, Merck submitted the third of three post-marketing commitment studies (HAV-068) to the BLA to provide safety and immunogenicity data which support coadministration of VAQTA with DTaP and *Haemophilus influenza b*, as well as to increase the total safety database for administration of two doses of VAQTA in children 12-23 months of age, thus satisfying all post-marketing commitments designated in the VAQTA approval letter of August 11, 2005.

The second part of this supplement includes pooled safety data from five studies (HAV-043, HAV-057, HAV-066, HAV-067, and HAV-068), assessing safety and immunogenicity of VAQTA given with or without concomitant childhood vaccines in at least 3000 children in the second year of life. These pooled safety data were reviewed, and no safety signal was identified which would preclude continued administration of VAQTA to children as young as 12 months of age. All five studies in this supplement were conducted in the U.S.

3. Chemistry Manufacturing and Controls (CMC)-Serology Assay Reviews

There were no changes in the product within this supplemental BLA.

Full CMC review of VAQTA was initially completed at the time of original licensure in 1996. Over the ensuing years, all lots of vaccine used in the concomitant study were reviewed and released for distribution by CBER.

The CMC reviews in this supplement focused on the assays used to evaluate the immune response to each of the antigens included in the vaccines administered in the study. Because assessment of potential diminution of the immune response was one of the primary goals of the study, assessments of serology assay validations for hepatitis A, *Haemophilus influenza b*, and pertussis antigens (PT, FHA, and PRN) were an essential part of the review of this supplement. No interference of immune responses to diphtheria and tetanus was observed when the fourth dose of DTaP (Infanrix in study 068) administered with or without VAQTA, and these results were considered confirmatory of results of immune responses to diphtheria and tetanus antigens in study 057.

The assays for the serological responses to five separate antigens were considered. Separate reviews were performed for the immune response assay for each of the following sets of antigens:

1. **Hepatitis A:** Antibody response to hepatitis A was determined by ---(b)(4)------. The sponsor submitted reports on the ---(b)(4)----- assay and a detailed analysis of assay variability. These were found to be acceptable, and the assay was assessed as acceptable for the testing performed in study HAV-068.[1]
2. **Diphtheria:** Evidence was provided that the ---(b)(4)-- based ----(b)(4)----- assay to detect anti-diphtheria antibodies demonstrated suitable precision for calculating study endpoints. This was further supported by the fact that 100% of subjects in both concomitant and non-concomitant groups achieved levels 4-fold higher than the conventionally accepted seroprotective level for antibody response of ≥ 0.1 IU/mL, 1 month post-vaccination. The results of this analysis provided confirmation of results of immune response to the fourth DTaP when administered with or without VAQTA as reported in study HAV-057 which supported initial approval of use of VAQTA in children 12-23 months of age.
3. **Tetanus:** On initial review, it appeared that the data for the tetanus antibody assay would be sufficient to confirm the results for anti-tetanus antibody response after the fourth dose of DTaP. CBER agreed to allow Merck to submit the data for D and T after the fourth dose of DTaP (as administered in study 068) and accept these data as confirmatory of results from study 057. No formal statistical comparisons were required. However, 100% of subjects in both the concomitant and non-concomitant groups achieved a level of at least 25 times greater than the conventionally accepted seroprotective level of ≥ 0.1 IU/mL for tetanus, 1 month post-vaccination. Results were similar in the full analysis population. However, upon review of additional data for the tetanus results requested by CBER and submitted on November 18, 2011 [STN 103606/5469.5004), the CMC reviewer noted that two different tetanus assays were utilized during the course of the study. On December 14, 2011, the tetanus assay CMC reviewer requested additional information regarding the two assays used in the course of this study in order to assess concordance of these two assays, i.e., that the two assays gave similar results, and that there was no evidence of bias from use of the two assays. A telecon was held between CBER and Merck on January 9, 2012 in order to provide further clarification of the CBER request. Merck responded on February 23, 2012. From review of these data, the CMC reviewer for the tetanus assay noted that the 2010 results were 2.5-fold lower than those assayed in 2009. In a subset analysis provided by Merck where subjects' pre-vaccination and post-vaccination blood samples utilized the same assay, 100% of subjects in each group (approximately 50 subjects who received concomitant Infanrix plus PedvaxHIB plus VAQTA and approximately 50 subjects who received Infanrix plus PedvaxHIB without VAQTA) were seropositive with titers ≥0.1 IU/mL of anti-tetanus antibody. Therefore, no evidence of interference in immune responses to tetanus (or to hepatitis A) was noted when Infanrix and PedvaxHIB

[1] The hepatitis A assay reviewer noted that during review of a separate sBLA (125108/341) in 2009, in which this hepatitis A assay was also reviewed, Merck made a commitment that for new protocols requiring anti-hepatitis A testing, a formal validation package for the anti-hepatitis A serology assay would be submitted to the IND for review prior to testing. The clinical study associated with this BLA supplement was initiated prior to 2009.

were administered concomitantly with VAQTA or when Infanrix and PedvaxHIB were administered non-concomitantly with VAQTA.

4. **Acellular pertussis:** Assay information for immune responses to pertussis antigens PT, FHA and PRN was submitted on November 18, 2011. The CMC reviewer for the pertussis antigen assays reviewed the submitted material and concluded that the pertussis (b)(4) assays to be sufficiently validated for their intended purpose.
5. **Anti-PRP antibody assay for *haemophilus influenza b:*** Additional information was requested regarding the assay on November 21, 2011 and a response was submitted on December 15, 2011 in STN 103606.5469.5006. The data were reviewed and assessed as acceptable for the purposes of this supplement.

4. Preclinical Pharmacology/Toxicology

Not applicable.

5. Clinical (Immunogenicity and Safety)

The following materials were considered in the review of this supplement: 1) datasets from study HAV-068 for assessment of immunogenicity and safety of administering the VAQTA alone, VAQTA dose 1 concomitantly administered with DTaP and PedvaxHIB; VAQTA dose 1 administered at 30 days after administration of DTaP and PedvaxHIB given together; 2) datasets for combined safety datasets from studies HAV-043, HAV-057, HAV-066, HAV-067, and HAV-068 for assessment of safety profile of VAQTA administered alone as compared to concomitant administration with other childhood vaccines; anti-hepatitis A antibody assay validations; anti-pertussis antibodies (PT, FHA, and PRN) assay validations; anti-diphtheria antibody assay validation; anti-polyribosylribitol phosphate (PRP) antibody assay for *Haemophilus influenza b;* and anti-tetanus antibody assay data. Studies HAV-043 and HAV-057 supported approval of VAQTA administration in children as young as 12 months of age [August 11, 2005]; study HAV-066 provided safety data for administration of two doses of VAQTA in an additional 2260 children 12-23 months of age; study HAV-067 supported coadministration of VAQTA with Prevnar and ProQuad in children during the second year of life based on results of safety and immunogenicity analyses [March 30, 2010]; and study HAV-068 is considered supportive of coadministration of VAQTA with DTaP (Infanrix) and Hib (PedvaxHIB) vaccines in children during the second year of life [present supplement]. Taken together with studies HAV-043 and HAV-057 in the present supplement, safety data was provided in more than 3000 children 12-23 months of age, and fulfills the remaining post-marketing commitments which were stipulated in the approval letter of August 11, 2005 at the following FDA website: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm110017.htm.

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STUDY HAV-068

Study HAV-068 was a randomized, controlled, open label, multicenter, safety and immunogenicity trial of VAQTA given concomitantly with PedvaxHIB and Infanrix or PedvaxHIB versus the administration of VAQTA non-concomitantly with PedvaxHIB and Infanrix or PedvaxHIB in healthy children 15 months of age.

Protocol HAV-068 was divided into two stages: Stage I included the concomitant use cohorts (groups 1-4), and randomized 1:1 concomitant:non-concomitant administration of VAQTA with the other childhood vaccines. Stage II included Cohort 5, in which children were administered two doses of VAQTA without other vaccines. Stage I study design is shown in Table 1, and Stage II study design is shown in Table 2.

Table 1: Study HAV-068, Stage I Study Design

Group	Cohort	Visit/Age	Visit/Age	Visit/Age	Visit/Age	Visit/Age	Visit/Age
		Visit 1¶	Visit 2	Visit 3	Visit 3	Visit 4	Visit 4
		Day 1 (15M)	Week 4 (16 M)	Week 24† (~21 M)	Week 28† (~28 M)	Week 28 (~22 M)	Week 32 (~23 M)
VIP‡ n=310	1 (Concomitant) n=155	VAQTA+ Infanrix+ PedvaxHIB (Bleed)	(Bleed)	VAQTA	NA	(Bleed)	NA
	2 (Non-concomitant) n=151	Infanrix+ PedvaxHIB (Bleed)	VAQTA	(Bleed)	NA	VAQTA	NA
VP§‖ n=310	3 (Concomitant) n=159	VAQTA+ PedvaxHIB (Bleed)	(Bleed)	VAQTA	NA	(Bleed)	NA
	4 (Non-concomitant) n=152	PedvaxHIB (Bleed)	VAQTA (Bleed)	NA	VAQTA	NA	(Bleed)

†Dose 2 VAQTA must be administered at least 24 weeks following dose 1. Groups 1 and 3 should be administered the second dose of VAQTA at Week 24 and Groups 2 and 4 should be administered the second dose of VAQTA Week 28.

‡Subjects in the VIP cohort will have previously received Infanrix or Pediarix for the primary DTaP vaccination series during the first year of life. Pediarix is a multivalent vaccine comprised of hepatitis B, polio, and the DTaP components of Infanrix. Subjects will also have received PedvaxHIB/COMVAX or ActHIB, but not both, for the primary Hib vaccination series.

§Subjects in the VP cohort will have received PedvaxHIB/COMVAX or ActHIB, but not both, for the primary Hib vaccination series. Prior DTaP vaccination history will not be considered for inclusion into the VP cohort.

‖DTaP vaccine will not be administered within the study protocol, but can be administered after safety follow-up is obtained after the Week 4 vaccination visit and up to 14 days prior to the Week 24 or Week 28 visit, since it is a non-live vaccine, or after the blood sample is drawn postdose 2 VAQTA for all groups in Cohort 2.

¶Concomitant administration of PedvaxHIB and Infanrix is allowable per product labels.

Source: Table 1 adapted from sBLA 103606/5469.5001, 5.3.5.1, CSR HAV-068, p. 33

Table 2: Study HAV-068, Stage II Study Design

Cohort	Group	Vaccination & Blood Draw3 Time Points (Approximate Age)			
		Visit 1	Visit 2	Visit 3	Visit 4
		Day 1 (12-17M)	Week 2	Week 24 (18-24M)	Week 26 (2 weeks postdose 2)
VAQTA	5 n=654	VAQTA	(Return VRC)	VAQTA	(Return VRC)

A subject could receive the second dose of VAQTA more than 6 months after the first dose, but prior to 24 months of age.

Source: Table 2 adapted from sBLA 103606/5469.5001, 5.3.5.1, CSR HAV-068, p. 34

Subject Accounting

- A total of 1271 subjects were enrolled at 58 study sites in the U.S., and all subjects received at least one study vaccine.
  - Stage I: A total of 617 subjects received at least one dose of vaccine: 314 subjects were included in the concomitant groups (numbers 1 and 3) and 303 subjects were included in the non-concomitant groups (numbers 2 and 4).
  - Stage II: A total of 654 subjects received at least one dose of vaccine.

- The gender distribution of subjects study HAV-068 was generally balanced:
  - Stage I: Of the 617 subjects participating in Stage I, 54.0% were male and 46.0% were female.
  - Stage II: Of the 654 subjects participating in Stage II, 51.2% were male and 48.8% were female.

- The race distribution of subjects in study 068 was as follows:
  - Stage I: 63.9% White; 17.5% Hispanic American; 14.7% Black; 1.3% Asian; and 2.6% other.
  - Stage II: 66.1% White; 10.6% Hispanic American; 16.8% Black; 1.3% Asian; and 5.0% other.

Immunogenicity in Study HAV-068

Table 3 presents the pre-specified primary endpoints for hepatitis A, Hib, and pertussis antigens (PT, FHA, and pertactin). As noted, results of immune responses to diphtheria and tetanus would be observational and considered confirmatory of the immune responses to diphtheria and tetanus as previously reported in study HAV-057.

Table 3: Study HAV-068 – VAQTA, Hib and Pertussis (PT, FHA, and pertactin) Primary Endpoints and Non-Inferiority Criteria

Vaccine Component	Endpoint	Group comparison	Non-Inferiority Criteria for Primary Endpoints and Comparisons for secondary endpoints
Hepatitis A	**PRIMARY** Seropositivity rate [SPR] @ 4 weeks postdose 2 (percent ≥10mIU/mL)	CONCOMITANT [1&3] minus NONCONCOMITANT [2&4]	LB of the 95% CI around the difference in SPRs is >-10%
	SECONDARY GMTs @ 4 weeks postdose 2	CONCOMITANT [1&3] divided by NONCONCOMITANT [2&4]	(Fold difference and 95% CI)
	EXPLORATORY Seropositivity rate [SPR] @ 4 weeks postdose 2 (percent ≥10mIU/mL)	CONCOMITANT [1&3] minus NONCONCOMITANT [2&4]	(LB of the 95% CI around the difference in SPRs is >-5%)
Hib (PRP)	**PRIMARY** Antibody Response rate @ 4 weeks postvaccination (percent > 1.0µg/mL)	CONCOMITANT [1&3] minus NONCONCOMITANT [2&4]	LB of the 95% CI around the difference in SPRs is >-10%
	SECONDARY GMTs @ 4 weeks postvaccination	CONCOMITANT [1&3] Divided by NONCONCOMITANT [2&4]	(Fold difference and 95% CI)
Pertussis (PT, FHA, pertactin)	**PRIMARY** GMTs @ 4 weeks postvaccination	CONCOMITANT [1] divided by NONCONCOMITANT [2]	LB of the 95% CI around the ratio of GMTs (Group 1/Group 2) >0.5 for each antigen (excludes a decrease of 2-fold or more)

GMC=Geometric Mean Concentration; GMT=Geometric Mean Titer
SPR = seropositivity rate
Group 1: VAQTA 1+Infanrix+PedvaxHIB (Day 1) →VAQTA 2 (Week 24)
Group 3: VAQTA 1+PedVaxHIB (Day 1) → VAQTA 2 (Week 24)
Group 2: Infanrix+PedvaxHIB (Day 1) → VAQTA 1 (Week 4) → VAQTA 2 (Week 28)
Group 4: PedvaxHIB (Day 1) → VAQTA 1 (Week 4) → VAQTA 2 (Week 28)

Diphtheria and Tetanus: GMTs and percent of subjects achieving antibody titer ≥ 0.1 IU/mL were compared in the concomitant group (Group 1) as compared to the non-concomitant group (Group 2).

Analysis Cohorts

Per-Protocol Analysis Set

- **Hepatitis A:** The **per-protocol population** consisted of all Stage I subjects who received vaccinations within the specified day ranges, completed appropriate follow-up, had any baseline serostatus, and were without any pre-specified protocol violations.
- **Hib:** For analyses involving Hib, the interest was primarily in those who had valid post-vaccination serological measurements within specified day ranges.
- **Pertussis:** For analyses involving the pertussis components of Infanrix, the interest was primarily in those who had valid serological measurements within specified day ranges both pre- and post-vaccination.

Immunogenicity Results: The per protocol analysis set was the primary analysis population for assessment of non-inferiority and comparisons of immune responses for all antigens. Further, the results for the following analyses in the per protocol analysis set were comparable to analyses conducted in the subjects with all serology set and the full analysis set.

- **Hepatitis A:**
  - **Primary endpoint:** The immune responses (seropositivity rates) to hepatitis A antigen at 4 weeks after receipt of dose 2 VAQTA after concomitant administration of VAQTA (dose 1) with Infanrix and PedvaxHIB or VAQTA (dose 1) with PedvaxHIB was non-inferior (100% [95% CI: 98.2, 100%]) to the immune response to hepatitis A antigen when VAQTA (doses 1) was administered alone (100% [95% CI: 98.0, 100%]). The difference in seropositivity rates was 0% [95% CI: -1.8, 2.1%] thus meeting the non-inferiority criterion to rule out a decrease of 10 percentage points or more.

  - **Secondary endpoint:** Secondary analysis in the PPE assessing fold-difference at 4 weeks after dose 2 VAQTA demonstrated that the GMT ratios for the concomitant groups (GMT = 3526.5) and non-concomitant groups (GMT = 4674.3) were non-inferior (ratio 0.8 [95% CI: 0.6, 0.9]) since the decrease was less than 2-fold (and the lower bound of the 95% CI around the fold difference was > 0.5).

- **Haemophilus influenza b [Hib] (Polyribosylribitol Phosphate [PRP]):**
  - **Primary endpoint:** The PRP antibody response rates to Hib (PRP) were non-inferior when PedvaxHIB was coadministered with VAQTA (dose 1) and Infanrix or when PedvaxHIB was coadministered with VAQTA (dose 1) (97.7%) as compared to the immune response to Hib (PRP) when PedvaxHIB was coadministered with Infanrix only (97.1%). The difference in response rates between the concomitant and non-concomitant groups was 0.6% [95% CI: -2.8,

4.1%] thus meeting the non-inferiority criterion to rule out a decrease of 10 percentage points or more.

- **Secondary endpoint:** Secondary analysis in the PPE assessing fold-difference 4 weeks post-vaccination demonstrated that the GMT ratios for the concomitant (GMT = 18.6) and non-concomitant groups (GMT = 17.6) were non-inferior since the decrease was less than 2-fold (and the lower bound of the 95% CI around the fold difference was > 0.5).

- **Pertussis antigens (pertussis toxin [PT], Filamentous Hemagglutinin Antibody [FHA], and pertactin):**
  - **Primary Endpoint:** Immune responses (GMT ratios) to pertussis antigens, including PT, FHA, and pertacttin, when Infanrix was coadministered with VAQTA and PedvaxHIB were non-inferior as compared to when Infanrix was coadministered with PedvaxHIB only. These analyses are presented in Table 4.

Table 4: Study HAV-068 – Fold Difference of anti-PT, anti-FHA, and anti-Pertactin GMT ratios for Pertussis in the Concomitant (Groups 1) divided by the Non-Concomitant (Groups 2), 4 weeks Post-Vaccination

	Group 1: Concomitant VAQTA+Infanrix+PedvaxHIB (N=154)		Group 2: Non-concomitant VAQTA separate from Infanrix + PedvaxHIB (N=150)		
Antigen Parameter	n	Estimated† Response	n	Estimated† Response	Fold Difference:† (Group 1) minus (Group 2) (95% CI)
PT GMT	85	68.6	83	54.0	1.3 (1.0, 1.7%)
FHA GMT	85	253.9	83	256.6	1.0 (0.8, 1.3%)
Pertactin GMT	85	345.8	83	330.1	1.0 (0.8, 1.4)

N = Number of subjects vaccinated; n = Number of subjects contributing to the per-protocol analysis for the given antigen.
GMT = Geometric mean titer; PT = Pertussis toxin; FHA = filamentous hemagglutinin antibody
†Estimated responses and their fold-difference were based on an ANCOVA model with the natural logarithm of the individual postvaccination titers as the response variable, and the natural logarithm of the prevaccination titer, treatment group (Group 1 or 2), and Hib vaccination history as fixed effects. Non-inderiority is computed based on a non-inferiority test to rule out a decrease of 2-fold or more.
The conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI on the fold-difference excluding a decrease of 2 fold or more. This indicates that the fold difference is statistically significantly less than the prespecified clinically relevant 2-fold difference at the 1-sided α =0.025 level.
Source: STN 103606/5469.5001, 5.3.5.1, CSR HAV-068, Table 11.9, p. 147

- **Diphtheria and Tetanus:** The immune responses (by seropositivity rates and GMTs) were comparable when Infanrix was coadministered with VAQTA (dose 1) and PedvaxHIB as compared to when Infanrix and PedvaxHIB were coadministered separately from VAQTA (dose 1), and confirm results of study HAV-057. In these analyses, 100% of subjects in the concomitant and non-concomitant groups achieved GMTs ≥0.1 IU/mL for antibodies to diphtheria and tetanus at four weeks after receipt of Infanrix. Additional subset results in which subjects in each group received VAQTA either concomitantly or non-concomitantly with Infanrix and stratified according to the tetanus assay method used also demonstrated that 100% of subjects achieved anti-tetanus antibody GMTs ≥0.1 IU/mL.

Regardless of the anti-tetanus test method used, there was no evidence of interference in immune responses to anti-tetanus antibodies when VAQTA was administered concomitantly or non-concomitantly with Infanrix and PedvaxHIB.

Safety in Study HAV-068

- **Stage I (Concomitant versus non-concomitant administration groups):** All subjects who were vaccinated and had safety follow-up data were included in the safety analyses and summaries. No subjects with safety data were excluded from the safety analyses. Groups 1 and 3 combined and Groups 2 and 4 combined were compared across the combined safety follow-up periods after Visits 1 and 2 (for a total of 28 days).

  Solicited events included fever, injection site redness and injection site swelling.

  Analysis of safety data included risk differences, 95% CIs for the risk difference, and p values for the comparisons of the treatment groups involving injection site AEs solicited on the VRC within Days 1 to 5. Analysis of safety data in Stage I also included comparison between treatment groups of temperatures collected within Days 1 to 5.

  - **Injection Site Adverse Events (5 days after vaccination)**
    - ***Solicited Adverse Events at the Injection Site of VAQTA:*** In the 5 days after dose 1 VAQTA, subjects in the concomitant group were 1.3 to 2.0 times more likely to experience at least one injection site AE as compared to subjects in the non-concomitant group. This appears to be driven primarily by pain at the injection site, the majority of which were categorized as mild. All other injection site AEs at the VAQTA site after the second dose VAQTA appear to occur with similar incidence in the concomitant and non-concomitant groups. The vast majority of pain was categorized as mild, and the majority of reported erythema and swelling measured ≤ 1 inch at the widest margin. Based on these data, there does not appear to be a clinically significant difference in VAQTA injection site AEs between the concomitant and non-concomitant groups.
    - ***Unsolicited Adverse Events at VAQTA Injection site:*** Injection site hematomas were the most frequently reported unsolicited injection site adverse events were observed in the concomitant (2.6%) and non-concomitant groups (2.3%) at similar rates, and the majority of these events were mild in intensity.
    - ***Solicited Adverse Events at the Injection Sites of PedvaxHIB and Infanrix:*** In the 14 days after vaccination, there were no statistically significant differences in the incidence of erythema, pain/tenderness, or swelling, and minor differences noted were likely of minimal clinical relevance.
  - **Systemic Adverse Events**
    - ***Solicited Systemic Adverse Events (Temperature 5 days after vaccination):*** Temperature data were converted and reported in the clinical study report as "oral equivalents" for both rectal (rectal T minus 1°F) and axillary (axillary T plus 1°F) temperatures. CBER conducted a review of raw data (i.e., temperatures recorded by parents/guardians prior to conversion to oral equivalent). These readings were tabulated by method obtained, i.e., rectal vs.

axillary, and by treatment groups (i.e., concomitant [groups 1 and 3] and non-concomitant [2 and 4].)

- The majority of subjects did not have fever by **axillary measurement** (89.3% concomitant and 87.7% non-concomitant), and there was a trend of decreasing incidence with increasing temperature range. There was a somewhat higher proportion of subjects with fever in the temperature range of ≥ 102.2°F (≥ 39.0°C) to < 103.1°F (≥ 39.5°C) in the non-concomitant group as compared to subjects in the concomitant group, but otherwise, incidence rates in all other ranges were similar in both groups.
- The majority of subjects did not have fever by **rectal measurement** (54.5% concomitant group and 53.0% in the non-concomitant group). There was a trend of decreasing incidence with increasing temperature range, and all incidence rates by rectal measurement were similar in the concomitant and non-concomitant groups.

✓ ***Unsolicited Systemic Adverse Events (28 days after vaccination):*** The proportion of subjects reporting at least one systemic adverse event overall was 56.3% (10/302) in the concomitant group and 56.0% (170/302) in the non-concomitant group; risk difference = 0.3% [95% CI: -8.6, 4.9%]. Systemic adverse events with the highest incidence rate overall in the concomitant and non-concomitant group included: pyrexia: 21.5% (65/302) concomitant versus 23.4% (68/291) non-concomitant group; risk difference = -1.8% [95% CI: -8.6, 4.9%]; irritability: 10.6% (32/302) concomitant versus 16.2% (47/291) non-concomitant; risk difference = -5.6% [95% CI: -11.1, -0.1]; and diarrhea: 9.9% (30/302) concomitant versus 9.6% [28/291] non-concomitant; risk difference 0.3% [95% CI: -4.6, 5.2]. The rates of unsolicited systemic adverse events in the 28 days after vaccination were similar in both the concomitant and non-concomitant groups. Only irritability occurred from 0.1% to 11.1% more frequently in the non-concomitant group as compared to the concomitant group.

- **Stage II (VAQTA administered alone):** For subjects receiving VAQTA alone, 72% (466/647) reported 1 or more adverse events, with 38.5% of subjects reporting an injection site adverse event and 61.1% reporting a systemic adverse event. Two subjects (0.3%) experienced a serious adverse event, both of which were considered definitely not related to study vaccine.
  - ***Injection Site Adverse Events, Solicited:*** In the 5 days after any dose of VAQTA, 38.0% (246/647) subjects reported any adverse event at the injection site, which included 24.9% after dose 1 VAQTA and 28.4% after dose 2 VAQTA. The majority of these local adverse events were mild in intensity, appear to be of minimal clinical significance and raise no safety concerns.
  - ***Injection Site Adverse Events, Unsolicited:*** In the 5 days after any dose of VAQTA, injection site hematoma was the most frequently reported unsolicited injection site adverse event (3.7% of subjects with 2.3% after dose 1 and 2.2% after dose 2). Again, the majority of those reported were mild in intensity.
  - ***Systemic Adverse Events, Solicited:*** In the 5 days after dose 1 and dose 2 of VAQTA, 9.4% and 8.6% of subjects, respectively, were noted to have a

temperature ≥ 100.4° F; 2.9% and 2.4% of subjects, respectively, were noted to have a temperature ≥ 102.2 ° F.

- ✓ ***Solicited Adverse Events in the 14 days after any dose of VAQTA:*** The proportions of subjects with injection site solicited adverse reactions in the 14 days after vaccination were almost identical to those reported in the five days after any dose of VAQTA (38.5%, 249/647). The proportions of subjects with any elevated temperature > 98.6 ° F in the 14 days after dose 1 and dose 2 VAQTA were 10.0% and 8.2%, respectively.

- ➢ ***Unsolicited Adverse Events in the 14 days after any dose VAQTA:*** The most common unsolicited adverse events in the 14 days after dose 1 and dose 2 VAQTA included: irritability (8.8% and 6.5%, respectively); rhinorrhea (6.2% and 3.8%, respectively); teething (5.7% and 4.3%, respectively); upper respiratory infection (4.9% and 5.2%, respectively); and diarrhea (4.6% and 3.8%, respectively).

Serious Clinical Adverse Experiences

Six subjects in study HAV-068 experienced nine serious adverse events. None of the events were assessed as related to study vaccines by the study investigators.

Deaths

There were no deaths reported in this study.

COMBINED SAFETY IN STUDIES HAV-043, HAV-057, HAV-066, HAV-067 AND HAV-068

Safety Database Children 12-23 months of age: Across five clinical trials, 4,374 children received one or two 25U doses of VAQTA, including 3885 children who received two doses of VAQTA and 1250 children who received VAQTA concomitantly with one or more other vaccines, including Measles, Mumps, Rubella Virus Vaccine, Live (MMR-II), Varicella Vaccine, Live (VARIVAX), Diptheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed (Tripedia or INFANRIX), Measles, Mumps, Rubella, and Varicella Vaccine, Live (ProQuad), Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197}, Prevnar), or Haemophilus B Conjugate Vaccine (Meningococcal Protein Conjugate, PedvaxHIB).

Demographics: Overall, the race distribution of study subjects was as follows: 64.7% Caucasian; 15.7% Hispanic-American; 12.3% Black; 4.8% other; 1.4% Asian; and 1.1% Native American. The distribution of subjects by gender was 51.8% male and 48.2% female.

Safety in Combined Studies

Solicited Injection Site Adverse Reactions in the five days after vaccination in studies HAV-066, HAV-067, and HAV-068

The most common local adverse reactions at the injection site of each any dose of VAQTA in the five days after any VAQTA injection, whether administered alone or concomitantly with other pediatric vaccines, included pain redness and swelling. Since ascertainment methods of safety were very similar for studies HAV-066, HAV-067 and HAV-068, the combined results for these three studies are presented in this summary

basis of approval. After Dose 1 VAQTA, the proportions of subjects with pain, redness and swelling in the non-concomitant and concomitant groups were 25% and 28.2%, 13.4% and 14.0%, and 7.7% and 10.0%, respectively. After Dose 2 VAQTA, the proportions of subjects with pain, redness and swelling in the non-concomitant and concomitant groups were 27.2% and 23.1%, 15.3% and 14.3%, and 8.4% and 8.2%, respectively. The results for individual studies were reviewed. In the package insert, results for studies HAV-067 and HAV-068 were presented individually, and the proportions of subjects with solicited local reactions were generally similar to the results observed for the combined studies. Over all studies, ≤0.3% of subjects experienced injection site adverse reactions graded as severe in intensity.

Pyrexia in the five days after vaccination in studies HAV-066, HAV-067, and HAV-068
Occurrence of pyrexia (Temperature ≥ 100.4°F and Temperature ≥ 102.2°F) in the five days after each and any dose of VAQTA was assessed in studies HAV-066, HAV-067, and HAV-068. After any dose of VAQTA, Temperature ≥ 100.4°F was recorded in 15.9% of the non-concomitant group and 18.9% of the concomitant group; Temperature ≥ 102.2°F was recorded in 4.4% of the non-concomitant group and 5.1% of the concomitant group. The difference in occurrence lower grade temperature elevations after any dose VAQTA was explained by a higher proportion of subjects developing temperature ≥ 100.4°F after receipt of dose 1 VAQTA with either ProQuad, ProQuad and Prevnar or Infanrix and PedvaxHIB. There were no differences noted in the proportion of subjects with Temperature ≥ 102.2°F after dose 1 VAQTA was administered with these other pediatric vaccines. No differences in either lower grade or higher grade temperature elevations were reported after dose 2 VAQTA.

Systemic Adverse Events in the 14 days after vaccination in all studies
Overall, when considering studies HAV-043, HAV-057, HAV-066, HAV-067 and HQAV-068 combined, 55.7% of subjects reported one or more systemic adverse event in the 14 days after receipt of any dose of VAQTA. The most common systemic adverse events after any dose of VAQTA were pyrexia (19.9%), irritability (10.6%), upper respiratory tract infection (7.9%), diarrhea (7.7%), rhinorrhea (6.7%), cough (6.2%), and otitis media (5.2%). Compared to subjects who received VAQTA alone (16.4%), those receiving VAQTA concomitantly with other pediatric vaccines experienced higher rates of pyrexia (27.0%) (pyrexia was defined across all studies as temperature ≥ 98.6°F or 'feverish' feeling). This difference in rates was also explained by higher rates of lower grade temperature elevations in subjects who received dose 1 VAQTA concomitantly with other childhood vaccines as compared to subjects who received dose 1 VAQTA alone. No differences in low-grade temperature elevations were observed in either group after receipt of dose 2 VAQTA.

Serious Clinical Adverse Experiences throughout all studies
Serious adverse experiences were tabulated from the combined safety dataset for studies 043, 057, 066, 067 and 068. Most of the serious adverse experiences in 12-23 month old subjects were assessed as not related or probably not related to study vaccine. In the majority of subjects who received VAQTA alone or VAQTA with other vaccines, other

illnesses or conditions were identified that accounted for these serious adverse experiences. No safety signal was identified from review of the combined safety data.

Deaths across studies
One death occurred in study HAV-066 in a 21 month old child with an underlying medical history of plagiocephaly, spastic quadriparesis,and microcephalus who died 75 days after dose 2 VAQTA due to a cerebrovascular accident. This death was assessed by the investigator as unrelated to administration of VAQTA, but assessed as more likely was related to the child's pre-existing conditions.

6. Statistical Review
No issues were identified by the statistical reviewer which would preclude approval of this supplement.

7. Clinical Pharmacology
See section 5 of this SBRA.

8. Advisory Committee Meeting
There were no product-specific concerns that would have benefited from an advisory committee discussion.

9. Other Relevant Regulatory Issues
Pediatrics
Safety and immunogenicity data from study HAV-068 included in this supplement satisfactorily fulfill STN 103606/5049 post-marketing commitment #4 (approval letter dated August 11, 2005). Further, combined safety data from studies HAV-043, HAV-057, HAV-066, HAV-067 and HAV-068 satisfactorily fulfill STN 103475/5048 post-marketing commitment #1 (approval letter August 11, 2005) and Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) requirements. Since post-marketing commitments #2 and #3 were was fulfilled by studies HAV-066 and HAV-067 (STN 103606/5374), all four post-marketing commitments have now been fulfilled, and no further concomitant administration pediatric studies will be required by the Agency at this time.

10. Bioresearch monitoring (BiMO) inspections
No issues were identified during BiMO inspections which would impact on approval of this supplement.

11. Labeling
The package insert was revised to include safety (section 6 Adverse Events) and immunogenicity data (section 14.7 for study HAV-068). The total number of subjects 12-23 months of age was updated in section 6 Adverse Events. In addition, section 7 Drug Interactions was also revised to include appropriate statements for coadministration of VAQTA with DTaP and *Haemophilus influenzae b* vaccine. Other changes were made to update the package insert.

12. Recommendations

The immunogenicity and safety data submitted in this BLA supplement support the concomitant administration of VAQTA with Infanrix and PedvaxHIB among children 12-15 months of age. For all five studies conducted in children 12-23 months of age, safety data were provided for approximately 4,374 children who received VAQTA, administered alone or concomitantly with other childhood vaccines in the second year of life [including Measles, Mumps, Rubella Virus Vaccine, Live (MMR-II), Varicella Vaccine, Live (VARIVAX), Diptheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed (Tripedia or INFANRIX), Measles, Mumps, Rubella, and Varicella Vaccine, Live (ProQuad), Pneumococcal 7-valent Conjugate Vaccine (Diphtheria $CRM_{197,}$ Prevnar), or Haemophilus B Conjugate Vaccine (Meningococcal Protein Conjugate, PedvaxHIB]. Based on review of these data, the review committee recommends approval of the BLA supplement.